Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 40, No. 1, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)01913-7

VIEWPOINT

Physicians' Interpretation of "Class Effects"

A Need for Thoughtful Re-Evaluation

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The concept of pharmacologic "class effects" exists across a broad range of medical products and is particularly pervasive with regard to cardiovascular agents. Evolution of the concept over the past two decades has shown the influence of physicians' practice patterns, pharmaceutical companies, health maintenance organizations and the Food and Drug Administration (FDA). Understanding the evolution of health care, social and economic policies, acknowledging the correction of medical misconceptions and inaccurate understanding and appreciating the emergence of new medical knowledge over the past decade should modify the clinician's viewpoint of "class effects." These revelations should signal caution in extrapolating the outcome efficacy or safety of one agent to another within a pharmacologic class. The authors urge clinicians, pharmaceutical companies, health maintenance organizations and the FDA to re-examine their concept of "class effects." An appeal is made for physicians to prescribe those pharmaceutical agents with definitive evidence of mortality and morbidity efficacy and safety established by appropriately scaled randomized clinical trials. (J Am Coll Cardiol 2002;40:19–26) © 2002 by the American College of Cardiology Foundation

Over the past two decades, there has evolved a clinical description applied to pharmacologic agents know as "class effects." An early example of the inception of this term was the antiarrhythmic classification of Vaughn-Williams et al. (1) to describe the electrophysiologic characteristics of various antiarrhythmic medications. By grouping antiarrhythmic drugs with similar electrophysiologic actions into classes I to IV, one could crudely generalize the electrophysiologic mechanisms of various pharmacologic agents (2). This classification with some limitations nonetheless proved to be clinically valuable in describing the electrophysiologic effects of antiarrhythmic agents (3). There was no relationship of the antiarrhythmic classification to the ultimate outcome benefits that patients might derive from such therapy.

During the late 1980s and early 1990s, the importance of neurohumoral stimulation in heart failure (HF) was realized and led to the development of therapeutic agents that interfere with the compensatory, but sometimes deleterious, effects of the renin-angiotensin-aldosterone system. Early randomized clinical trials in patients with congestive HF demonstrated the important beneficial hemodynamic changes associated with angiotensin-converting enzyme (ACE) inhibitors, called attention to their ventricular remodeling properties and documented their benefit in reducing mortality and morbidity (4). When several randomized ACE inhibitor clinical trials employing different ACE inhibitor agents demonstrated similar changes in surrogate end points and similar mortality and morbidity outcomes, there emerged an intuitive extrapolation and general conclusion that ACE inhibitors possessed a "class effect" that extended to all ACE inhibitors (5,6). Subsequently, new ACE inhibitors appeared in the therapeutic marketplace with a focus on surrogate end points. Whereas physicians initially believed that all ACE inhibitors were essentially the same except for varying pharmacologic properties, now, at the turn of the millennium, scientific knowledge of the variances of half-life, degree of lipid solubility, route of elimination, tissue levels and dose-response relationships indicate that different outcomes may result from specific ACE inhibitors (7–9). While some ACE inhibitor trials failed to show benefit, those ACE inhibitors with long half-lives and tissue penetration resulted in the most impressive clinical data relative to event reduction (7–9). Nonetheless, caution expressed to the casual acceptance of "class effects" had little impact on the spread of the broad medical concept (9,10).

Although the acceptance of "class effects" was promulgated by a variety of forces across the health care field, it is a precarious concept that is fraught with dubious interpretation. It is important for physicians to thoughtfully re-evaluate the data for "class effects" and reflect on the concept in light of recent discoveries of incomplete or inaccurate medical knowledge and new emerging science. These insights have brought forth a new emerging clinical tenet in the treatment of patients that admonishes "prescribing the right medication in the right population" (11). These developments are examined in this manuscript.

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Manuscript received October 24, 2001; revised manuscript received March 28, 2002, accepted April 8, 2002.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
AMI	= acute myocardial infarction
BEST	= Bucindolol Evaluation Survival Trial
CIBIS	= Cardiac Insufficiency Bisoprolol Study
CONSENSUS	= Cooperative New Scandinavian Enalapril Survival Study
COPERNICUS	= Carvedilol Prospective Randomized Cumulative Survival trial
FDA	= Food and Drug Administration
HF	= heart failure
HMO	= health maintenance organization
MERIT-HF	= Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
MIRACL	= Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study
NYHA	= New York Heart Association

SOCIETAL AND ECONOMIC INFLUENCE FOR BELIEF IN "CLASS EFFECTS"

Interestingly, several groups within the health care field for varying reasons quickly adopted the rationale of "class effects." Physicians seemed to readily adopt the reasoning of "class effects" because it certainly made life easier in the pragmatic daily world of clinical medicine. Not only is it difficult for a busy clinician to stay abreast of emerging clinical trials, but, when the early results of randomized clinical trials seem to indicate similar clinical outcomes for more than one agent within a drug class, it appeared reasonable to conclude that the benefits of such agents extended to all the drugs within that class. Unfortunately, practicing physicians have been shown to not always be aware of clinical trial results or appropriate therapeutic interventions established by evidence-based medicine (12), and the "lumping together" of clinical trial results by "class effects" provided a convenient way of understanding new agents within a pharmacologic class. Occasionally, there occurred an obstacle to this ideology, as for example with the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) II (13). After the demonstration of oral ACE inhibitor therapy rendering mortality benefit in the CONSENSUS I trial, physicians were surprised to learn that the administration of intravenous enalapril in the CONSENSUS II trial resulted in increased mortality and adverse events in patients with acute myocardial infarction (AMI) (13). Physician practice patterns reflected a delay in the early utilization of ACE inhibitors in patients with AMI as the Consensus II data were examined. Subsequent trial data analysis of CONSENSUS II concluded that the adverse events likely resulted from the proischemic effects of hypotension secondary to the intravenous administration of enalapril and the possible interaction of age as a confounding factor, which resulted in the increased mortality (13,14). This conclusion was indirectly reinforced by the beneficial findings from other orally administered ACE inhibitor trials in AMI (15,16), and the latter acceptance tended to entrench the idea that "class effect" outcomes (at least for oral ACE inhibitors) really existed.

Pharmaceutical companies embraced the concept of "class effects" for several reasons. Early in the 1990s, companies with new "me too" pharmaceutical agents that demonstrated similar properties for surrogate end points began to state that there was limited value in establishing the outcome benefit of their specific agent with a randomized clinical trial because it possessed "class effects" outcome benefits (17). The Food and Drug Administration (FDA) contributed, in part, to this strategy by the use of the vaguely defined term "class labeling." These attitudinal changes occurred during a time when medical focus had emerged on the principles of evidence-based medicine (18). Pharmaceutical companies were, more often than not, being confronted with the challenge of performing randomized clinical trials to establish the efficacy and safety of specific agents. Notwithstanding the immense societal and medical benefits that have resulted from the pharmaceutical industry at large, it nevertheless is a business entity that seeks to achieve profits and appease shareholders. With a claim of "class effects" and the nonperformance of randomized clinical trials, a pharmaceutical company could save a substantial amount of economic resources and competitive time to the marketplace with regard to a specific agent. The fact that randomized clinical trials are expensive, often require prolonged periods of time to execute and follow outcomes and demand rigor in their design and execution can pose a daunting burden to a pharmaceutical company (17). Fortunately for society and the medical profession, this challenge has been successfully undertaken by many in the pharmaceutical industry. In contrast, some pharmaceutical companies resorted to a marketing strategy of suggesting outcome benefits of their product based on "class effects" and emphasized the superiority of their product based upon efficacy measured by changes in specific surrogate end points (e.g., enhanced blood pressure reduction or cholesterol lowering). Alternatively, they may have demonstrated beneficial changes in small mechanistic trials directed at new surrogate end points (e.g., forearm vascular resistance or prostacyclin production) with a claim of "class effects" to legitimize their product for outcomes benefit (19). These small mechanistic clinical trials, which are underpowered to detect morbidity or mortality outcome evidence, serve to provide a scientific stage for pharmaceutical agents before the medical community at large and create visibility of a new agent in the marketplace. More often than not, such trials or "marketing studies" are specifically directed at surrogate end points and frequently are presented at national scientific symposia to garner or continue interest in a specific product. Any negative or adverse data is rarely reported in the literature due to either the acknowledged influence of publication lag or bias of negative data (20,21), or, as reported, pharma-

ceutical sponsors attempt to delay or suppress publication, forbid it by contractual arrangement or attempt to influence the nature of the reported findings (22,23). This strategy has seemingly proved successful because the FDA has previously approved products based upon an agent's actions on surrogate end points (e.g., some statins or hypertensive agents) without definitive clinical outcome data (18). Cleverly, this strategy avoids the possible "down-side" of either the business goal or the moral dilemma imposed on a pharmaceutical company by the discovery of a nonefficacious or potentially harmful product. What if a specific agent did not result in beneficial outcomes? What if it was neutral or had adverse effects? What if its benefit was no greater than that of a generically available product at a fraction of the cost? These potential risks are also reflected in the relative reticence of some pharmaceutical companies to perform "head-to-head" randomized trials of a new agent against proven agents of a pharmacologic class for fear of being shown in any way less efficacious, thereby possibly affecting their market-share position. It appears that some pharmaceutical companies readily adopted the strategy that their specific drug showed similar changes in surrogate end points and, thus, inherently was entitled to the associated "class effect" beneficial outcomes without a need for additional testing in randomized clinical trials.

Surprisingly, physicians' practice patterns indicate that they embraced many of these untested products, apparently on the merit of a product's superior action on a specific surrogate end point or lack of adverse side effects, rationalizing that its clinical outcome efficacy was established by "class effects." Physicians became accustomed to encountering industry representatives presenting a new FDA approved medication that had demonstrated enhanced action against a surrogate end point or was less expensive but had limited outcomes data of efficacy or safety. Physician's practice patterns in prescribing such products thus subsequently seemed to endorse and entrench the philosophy of "class effects."

Finally, this process in some instances was readily embraced by health maintenance organizations (HMO) whose early primary emphasis was to deliver health care at reduced costs (24). Through a policy of some HMO formulary committees focusing on surrogate end points and adopting a belief in "class effects" (often at the exclusion or lack of inclusion of knowledgeable medical input), many HMOs chose the "cost-effective" ACE inhibitor or lipid-lowering agent of lowest price, rationalizing their putative "class effect" outcome benefits. Some HMOs were specifically targeted by industry as seeking the best price while demanding limited data of efficacy and safety. In the current environment of the new millennium, however, there is a focus of society and pending congressional legislation directed at HMOs with regard to the patient's rights, safety and the quality of care received from such organizations (25,26). Therefore, we might anticipate that future government attention will be focused on what standards are utilized by HMOs to select pharmaceutical agents for the benefit of patient care, and the spotlight will focus on pharmaceutical evidence-based medicine.

EVIDENCE FOR CAUTION IN INTERPRETING "CLASS EFFECTS"

After a reflective decade of "evidence-based medicine," what is a clinician's perspective on "class effects?" The authors believe physicians have encountered several aberrations to the broad medical concept of "class effects" that warrant thoughtful re-evaluation. The evidence for this viewpoint emanates from a historical perspective of beta-blockers, ACE inhibitors and lipid-lowering therapy. Randomized clinical trials of these pharmacologic agents illustrate how physician attitudes and practice patterns resulted from: 1) incomplete or inaccurate medical understanding, or 2) a failure to appreciate evolving new medical knowledge.

Incomplete or inaccurate medical understanding. The perplexity of the underutilization of beta-blocker therapy in cardiovascular disease has been previously detailed by the authors (27). A major aspect in the past that influenced physician attitudes concerning beta-blocker therapy was the widely held false belief that such therapy was contraindicated in patients with congestive HF (27). Although the Beta-Blocker Heart Attack Trial demonstrated that propranolol-treated patients with a history of HF received a 47% improved survival from sudden death and a 30% improved survival for total and cardiovascular mortality, these data were contrary to accepted medical dictum (28). There was a prevailing entrenched physician belief that beta-blocker therapy was deleterious in HF. Over the past decade, randomized clinical trials have provided substantial insight to the benefits of beta-blocker therapy, and physicians are increasingly prescribing these valuable agents (29). Nevertheless, there have been valid exceptions to this understanding (Table 1). An early obstacle encountered was the clinical trials of xamoterol, which demonstrated that beta-blocker agents possessing intrinsic sympathomimetic properties were deleterious or not beneficial for some population with HF (30–32). Subsequently, most authoritative physicians advised against the use of beta-blocker agents with intrinsic sympathomimetic activity for patients with cardiac disease (33), albeit mortality benefit has been shown for low-dose acebutolol in high-risk AMI patients (34,35).

A second obstacle arose when the under powered Cardiac Insufficiency Bisoprolol Study (CIBIS) I trial focused concern and attention on the fact that perhaps beta-blocker therapy was only beneficial in HF patients with nonischemic heart disease (36). Clinical opinion and speculation once again fell victim to unreliable "data-dependent" subgroup analyses of small-scale evidence (37). This concern was later dispelled when the CIBIS II and Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trials demonstrated unequiv-

Table 1. Beta-Blocker Therapy in Heart Failure*

Beta-Blocker Efficacy			Beta-Blocker Adverse Effects		
Trial	Population	NYHA Functional Class	Trial	Population	NYHA Functional Class
MDC (33)	383	I, II, III, IV	Xamoterol (30)	516	III, IV
CIBIS I (36)	641	III, IV	MEXIS (32)	210	II, III
U.S. Carvedilol (41)	1,094	II, III, IV	BEST (43)	2,708	III, IV
CIBIS II (38)	2,647	III, IV			
MERIT-HF (39)	3,991	II, III, IV			
COPERNICUS (48)	2,289	III, IV			

*Modern era of concomitant angiotensin-converting enzyme inhibitors on AII-receptor blockers, diuretics and/or digitalis.
BEST = Bucindolol Evaluation Survival Trial; CIBIS = Cardiac Insufficiency Bisoprolol Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival trial; MDC = Metoprolol Dilated Cardiomyopathy trial; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MEXIS = Metoprolol and Xamoterol Infarction Study; NYHA = New York Heart Association.

ocal benefit of beta-blocker therapy in more than 6,000 ischemic and nonischemic patients with mild-to-moderate HF randomized to beta-blocker therapy or placebo (38,39). Both ischemic and nonischemic beta-blocker-treated patients received a survival benefit of 30% to 35% from total or cardiovascular mortality and a 40% to 44% survival benefit from sudden death (38,39). Thereafter, physicians begin to "buy-in" to the idea that not only was beta-blocker therapy beneficial in patients with congestive HF, but perhaps beta-blockers possessed a "class effect" with the proviso caveat that this benefit did not extend to agents with intrinsic sympathomimetic effects. Whereas the specific agents used in CIBIS II and MERIT-HF employed a $beta_1$-selective beta-blocker, some investigators proposed, for theoretical reasons, that newer third-generation nonselective beta-blockers possessing peripheral vascular or alpha-blocking properties could possibly provide an even greater degree of efficacy (40–42).

Unfortunately, to the surprise and dismay of both investigators and the sponsors of the Bucindolol Evaluation Survival Trial (BEST) performed in 2,708 New York Heart Association (NYHA) functional class III and IV patients, essentially minimal or no benefit was found to result from the third-generation nonselective beta-blocker bucindolol (43). Additionally, the trial results indicated adverse effects in black and NYHA functional class IV patients (43–45). The BEST trial included 627 (23%) black patients who were randomized and stratified by race, gender, left ventricular ejection fraction and the absence of coronary artery disease (43). Analysis showed that the lack of mortality benefit in blacks was not due to a lack of myocardial functional recovery or neurohormonal response, and the trend toward increased mortality ($p = 0.097$) was associated with a significant race-treatment interaction (44). Given these results, the added pharmaceutical costs of prescribing a newer third-generation beta-blocker as compared with a less expensive second-generation beta-blocker employed in CIBIS II (bisoprolol) or MERIT-HF (metoprolol-XL), seems to portend the demise of bucindolol in the marketplace. The scientific reasons accounting for the divergent result of BEST are unknown, but clearly this large-scale clinical trial exposed physicians' incomplete medical understanding of beta-blocker therapy in patients with HF. Whereas early speculation centered about bucindolol's alpha-blocking properties, which proved deleterious in hypertensive HF patients (46,47), it is difficult to reconcile that suspicion with the subsequently reported benefit of carvedilol (also with alpha-blocking properties) in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial (48). In COPERNICUS, carvedilol-treated patients with NYHA functional class II to IV HF had 35% fewer deaths, and this benefit also extended to black patients (48,49). Speculation arose that carvedilol's nonselective beta-blockade and alpha-adrenergic blockade were particularly advantageous to blacks who have greater response to cardiac $beta_2$-adrenergic stimuli than whites (49–51). This explanation, however, fails to explain why bucindolol with similar pharmacologic properties was nonefficacious in BEST. A more likely explanation resides in differences resulting from genetic polymorphisms of enzymes responsible for drug metabolism or the adrenergic receptors themselves, which were responsible for this confounding outcome (52,53). The recent appreciation of racial and pharmacogenetic interaction are also suspected to account for the findings that blacks received no or limited benefit in the Study Of Left Ventricular Dysfunction trial when treated with the ACE inhibitor enalapril (54–56). Clearly, these enlightening developments highlight our incomplete knowledge of specific pharmaceutical agents within a pharmacologic class and engender a cautious attitude toward the medical generalization of "class effects," particularly for outcome efficacy or safety.

Evolving new medical knowledge. As indicated above, emerging new medical knowledge also encroaches upon the simplistic vanilla concept of "class effects" as shown from the randomized clinical trials of various ACE inhibitors. While early randomized clinical trials of ACE inhibitor drugs demonstrated similar beneficial outcomes in patients with left ventricular dysfunction, it was serendipitously discovered that ACE inhibitors also significantly decreased ischemic events (57). This surprising discovery (not in concert with the prevailing view of ACE inhibitors predominantly

affecting hemodynamic changes) was later confirmed in other randomized clinical trials (58,57). These events led to an appreciation of the tissue effects of ACE inhibitors. Subsequent investigations discovered new knowledge of the role of ACE inhibitors in tissue, their actions on inflammatory mediators and a variety of positive effects on the vascular endothelium (59–61). Clinical recognition that some ACE inhibitors seem to render benefit against sudden death while others did not (62), the finding that trandolapril reduced the incidence of atrial fibrillation (63) and the finding that ramipril in the Heart Outcomes Prevention Evaluation trial (64) provided primary and secondary preventive benefits to a diverse group of patients without evidence of HF or systolic dysfunction seems to highlight the variable effects of ACE inhibitors. The putative mechanisms that may account for these diverse actions are unknown but are directed towards the varying effects of specific ACE inhibitors in tissue and the vascular endothelium (7,64,65). Thus, while ACE inhibitors may share similar hemodynamic effects and clinical outcomes in patients with left ventricular systolic dysfunction, their tissue properties vary substantially. Differences in beneficial outcomes in populations with arrhythmias (62,63), suspected diastolic dysfunction (64) and diabetes (64) argue for a closer examination of the "class effect" concept. All ACE inhibitors are not the same (9,10).

The past decade has also witnessed an evolution of medical knowledge concerning vascular atherosclerosis and plaque rupture and the genetic and biochemical heterogeneity that exists in patients with coronary artery disease. Current medical knowledge has focused scientific attention on the interactive role of pharmacologic agents, especially the HMG-Coenzyme A reductase inhibitors (statins) and the multiple mechanisms of the atherosclerotic plaque and endothelial substrate (66,67). The role of specific statins on nitric oxide biosynthesis (68), smooth muscle cell synthesis of extracellular matrix and apoptosis (69–72), cytokine production by mononuclear cells (73), tissue factor biosynthesis (74) and perhaps other molecular and cellular mechanisms that stabilize plaque have come to the forefront. These mechanisms present a rationale for the resulting endothelial nitrous oxide-mediated vasodilation, anti-inflammatory and antithrombotic effects observed with statin therapy. These nonlipid mechanisms may be of great importance, especially in subjects prone to plaque rupture (66,67). However, new evidence has emerged that statins may differ substantially in their effects on liver metabolism (75), collagen production by smooth muscle cells (76,77), skeletal myolysis (78) and major histocompatibility complex-II-mediated T-cell activation or immunomodulation (79). Noteworthy in this regard has been the recent product withdrawal of cerivastatin from the marketplace, which was prompted by 52 deaths associated with rhabdomyolysis (80). In recently reported FDA data of statins (81), cerivastatin demonstrated an 80-fold increase of adverse events in comparison with other statins.

Previous pharmacogenetic data have defined that a patient's response to a drug may depend on one or more factors that vary according to the genetic alleles that an individual carries (11). Factors involved include drug absorption, drug distribution, drug metabolism and elimination, drug concentration at the target site and the number and morphology of target receptors (11). This data also corroborates reports of efficacy in patients with coronary artery disease whose outcomes for a specific statin therapy were correlated with gene variants involved in the drug's mode of action (81–84). Therefore, pathophysiologic mechanisms relative to atherosclerosis and its therapy have revealed themselves to be multifactorial and multidimensional and represent evolving new knowledge that was unanticipated.

Interestingly, these discoveries of complexity have not overridden the dominant practitioner's concept that all statins are the same and share "class effects" outcome benefits. Despite the more than 40,000 patients randomized to clinical trials of simvastatin (85), pravastatin (86–88) and lovastatin (89), which demonstrated significant benefits in reducing mortality and morbidity, the most commonly prescribed statin currently in the U.S. is atorvastatin without such clear evidence of benefit (90–92). Atorvastatin has recently been shown in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (92) that examined 3,086 patients with unstable angina pectoris or non–Q-wave myocardial infarction to be mainly beneficial for worsening angina with evidence of ischemia. Hard end points of death, nonfatal myocardial infarction or resuscitated cardiac arrest only showed nonsignificant trends favoring atorvastatin (92). Moreover, atorvastatin did not affect coronary events during the initial five weeks (which comprised 70% of total events), HF or the need for revascularization. Although atorvastatin did reduce the rate of nonfatal stroke (an uncommon event in the trial), the positive findings of MIRACL have been criticized as being far from definitive (93). Reflection upon the existing prescription popularity of atorvastatin without substantive outcome evidence of broad efficacy is testimony, in part, to the establishment of the surrogate low-density lipoprotein cholesterol therapeutic target, the power of marketing and the "class effects" concept and a disappointing commentary to physicians' practice patterns in prescribing medications based on evidence-based randomized clinical trials. These developments encourage the viewpoint that physicians should prescribe specific drugs used in clinical trials, at the target dosage, in a similarly defined population of patients, to obtain similar clinical outcome benefits (11). This recommendation is obviously counterintuitive to the broad concept of "class effects."

INTERPRETATION WITHOUT LARGE-SCALE EVIDENCE

The authors would be remiss if they did not indicate that the class divergence discussed (adverse or beneficial) ema-

nates from differences that sometimes are based on a relatively small number of events or populations relative to the size of the overall main clinical trials of a class of pharmacologic agents (37). Such may be the case for xamoterol, bucindololol, trandolapril or atorvastatin as discussed above. Even highly significant differences based on a relatively small number of events from selected clinical trials may prove unreliable evidence of the existence of any real difference (37,94). Besides the element of chance, important trial differences in study populations, outcome definitions and dosages employed could have accounted for differences in observed clinical outcomes. However, when one reflects on the xamoterol, bucindolol or cerivastatin experience, in a pragmatic sense, it seems highly unlikely that the respective pharmaceutical companies will pursue continued investigation of those agents. In contrast, it might be hoped in a "perfect world" that pharmaceutical companies would examine their data to determine if their specific product in a pharmacologic class is associated with unanticipated adverse or beneficial effects encountered in the class, for example, race-interaction, rhabdomyolysis or antiarrhythmic benefit. In the "real world," however, once an agent has received regulatory approval from the FDA and enters the marketplace, additional clinical trials exploring either adverse or beneficial divergence seem to be seldom undertaken.

CONCLUSIONS AND RECOMMENDATIONS

Understanding the evolution of medical, social and economic policies, acknowledging the correction of medical misconceptions and inaccurate understanding and appreciating the emergence of new medical knowledge over the past decade should modify the clinician's viewpoint of "class effects." These revelations should signal caution in extrapolating the outcome efficacy or safety of one agent to another within a pharmacologic class (8–11). Nevertheless, many pharmaceutical agents share similar clinical structures and physiologic actions on surrogate end points and, therefore, categorically reside in a specific pharmaceutical class. While it is of practical merit to conceptualize that drugs within a pharmacologic class may result in some similar physiological actions, experience has shown that evidence-based morbidity and mortality outcomes in disease populations may differ widely for agents within a class. Therefore, the authors urge clinicians, pharmaceutical companies, HMOs and the FDA to re-examine their concept of "class effects." An appeal is made for physicians' to prescribe those agents with definitive evidence of mortality and morbidity efficacy and safety established by appropriately scaled randomized clinical trials (10,11,18,37,94). Pharmaceutical companies should be encouraged to perform comparative (head-to-head) trials through policies of the FDA designed to limit the number of "me too" drugs, and HMOs should develop cost-effective pharmaceutical policies that incorporate the evidence of randomized clinical trials. Finally, the boundaries of "class effects" have not been clearly delineated. Although emerging knowledge may provide new insights regarding the generalization of outcome benefits, currently there is clear evidence that acceptance of the broad medical "class effect" concept is unwarranted. Like most complex issues, it probably is not an "all or none" concept but one that needs careful clarification. Recent editorial attention has indicated the susceptibility of physicians to "Faustian bargains" (95) hopefully "class effects" will not be one of them.

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